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DISEASES AND DISORDERS
OF MUSCLE FUNCTION *

DONALD McEACHERN

Chief of Neurological Service, Montreal Neurological Institute

I WOULD like to discuss with you tonight some disorders of muscular function in man. It would not be profitable to deal with all the muscular ailments. I shall deal, therefore, with several prototypes that illustrate the great range and variety of mechanisms that make a man's muscles sick.

Some of these conditions are rare—but let that not dismay you. Addison's disease is rare, but it has led to fantastic discoveries of the role of the adrenal cortex and the glandular chain in health and in disease. In like manner a knowledge of the mechanism of muscular disorders may illuminate many other fields of medicine and may clarify the manifold problems of muscular fatigue.

But let us not quickly divorce the muscle from its bride, the anterior horn cell. They form a unit in health, and also in diseases which we call neuromuscular disorders. Our conception of this unit is shown in Figure 1.

* Given October 10, 1950 before the 23rd Graduate Fortnight of The New York Academy of Medicine. From the Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute.

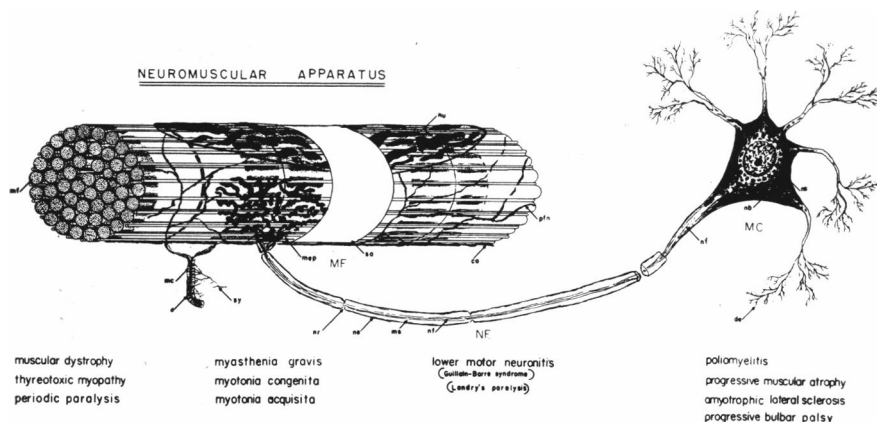


Fig. 1—Diagram of lower motor neurone. Main sites of disturbance in various diseases are shown.

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The term "Neuromuscular Disorders" includes the conditions which affect, in a systematic way, the anterior horn cell, the nerve fiber, the neuromyof junction, or the muscle fiber.¹ We group these together not upon anatomical grounds but because disturbance of one part of the lower motor neurone is apt to involve the other parts. Furthermore, their chemical processes and their vulnerability to noxae are often similar. Diseases quite different in causation may produce similar disturbances of function (e.g., pain, muscle spasm, fasciculation, atrophy). These often require skilled interpretation by specialized methods. Future advances in our understanding and treatment of these conditions must be based upon a knowledge of the physiology and chemistry of the lower motor neurone. Tonight, however, we will deal mostly with disorders of muscle.* You will hear about such strange things as myotonia, myasthenia, thyroidal muscular disorders, periodic paralysis and dystrophies, and I hope that you will find interest in them.

THE MYOTONIAS

Myotonia is a symptom. It consists in the prolonged contraction of

* The work to be described has been carried out over some years with the assistance of my colleagues Drs. Robert Pudenz, Guy Odom, Wolfgang Klemperer, William C. Gibson, Reuben Rabinovitch and G. Milton Shy.

a muscle, or a part of a muscle, after cessation of the stimulus—be it voluntary, mechanical or electrical. With a voluntary movement a whole group of muscles may remain in contraction for some seconds before relaxation sets in. A similar but very localized contraction follows stimulation of the muscle by percussion, an electrical shock or the prick of a needle. When a movement is repeated a number of times the muscles “warm up” and normal contraction and relaxation occur. The myotonia returns again after a period of rest. Myotonia may be demonstrable clinically in all the voluntary muscles, or it may be limited to a few, such as the thenar muscles and the tongue. In such cases, however, the more refined method of electromyography sometimes shows that the myotonia is more widespread.

Myotonia occurs with two rare but well recognized diseases—myotonia dystrophica and myotonia congenita. It has been reported also in association with myxoedema or hypothyroidism, and in these instances it responds to treatment with thyroid. It also occurs in goats as an hereditary disease which seems identical to myotonia congenita in humans.

What is the nature of myotonia? This has been a matter of debate for many years. Myotonia persists after blocking of the motor nerve and after spinal anaesthesia, thus indicating a peripheral mechanism. Recent electromyographic work has shown that the abnormality lies predominantly or altogether in the muscle.

Brown and Harvey² have studied the mechanism in myotonic goats. Electromyograms show a long-lasting, irregular tetanus. The response of the muscle to a single motor nerve stimulus is repetitive in nature. The myotonic response to mechanical stimulation is not diminished by full curarization, nor by section and degeneration of the motor nerve. Response and threshold to acetylcholine is the same in myotonic and normal muscle, but the response is much prolonged in the myotonic goat.

There are interesting relationships to potassium. Myotonic muscle is abnormally sensitive to the potassium ion. Epinephrine, which lessens the stimulation of striate muscle by potassium, reduces the myotonia of goats and of humans. Desoxycorticosterone, which influences potassium balance and lowers serum potassium, abolishes myotonia in the goat. Both epinephrine and desoxycorticosterone are capable of producing a fall of serum potassium and paralysis in persons subject to periodic paralysis.

Kennedy and Wolf³ suggested that myotonia and myasthenia gravis were clinical opposites because of their opposite reactions to neostigmine and quinine. They even went so far as to cross-transfuse two patients who had the respective diseases. No improvement occurred in either. The concept is interesting but does not fit all the facts. The supposition that myotonia may be due to increased liberation of ACh at the neuromyal junctions has no proof to support it.

The improvement of myotonia by quinine is due to its ability to suppress repetitive muscle responses of all types, and also to its curarizing action, which diminishes the number of impulses reaching the muscle fiber. Quinine is prescribed clinically for its symptomatic effect in reducing myotonia, and the drug can be given by mouth for this purpose.

We have recently discovered that myotonia is abolished by cortisone. Within four or five days the muscles become normally quick and agile. In one case of myotonia atrophica, for example, the electromyogram showed repetitive volleys lasting for one minute and sixteen seconds after the stimulus. This was reduced to zero on the fifth day of cortisone therapy. The myotonia returns, however, when the hormone is discontinued. Whether or not the underlying muscular defect in myotonia dystrophica can be influenced by cortisone requires further investigation.

MYASTHENIA GRAVIS

This extraordinary disease is characterized by weakness and undue fatigability of the skeletal muscles. Heart and visceral musculature is not involved. The patient is apt to have drooping eyelids, a blank, expressionless appearance, a nasal voice, and difficulty in chewing and swallowing. In severe cases there may be weakness and fatigability of the limb muscles so that arms and legs can scarcely be lifted. In extreme cases the respiratory muscles may be affected, and the patient dies of respiratory paralysis or spasm of the larynx. The above features resemble unmistakably the acute and evanescent effect of curare poisoning.

The character of myasthenia gravis is suggestive of an endocrine or metabolic disorder. Onset is usually after puberty and in early life. There is a tendency to remissions. Modifications of the disease may occur during pregnancy or with changes of thyroid function. At autopsy no structural change is found in the nerves or muscles save for the

presence of scattered lymphorrhages, which can scarcely be considered causative. The only other common finding is hyperplasia or tumor formation in the thymus, which occurs in a suggestive number of cases,⁴ viz., about 50 per cent of reported autopsies (weighted) and about 10 per cent of surgical explorations in unselected cases. Even the latter figure is high.

There are other similarities too between myasthenia gravis and curare poisoning. Numerous electromyographic studies indicate that in both conditions there is a sort of block to normal neuromuscular function. The motor nerve fibers conduct normally, and the response of muscle to direct stimulation is normal, but the transmitting machinery from motor end-plates to muscle does not function properly. Furthermore, both conditions respond dramatically to anti-cholinesterase drugs such as eserine and neostigmine. The myasthenic patient is made much worse by small doses of curare.

Let us examine the various possible derangements that might occur in the chemical transmitting mechanism from nerve to skeletal muscle. (a) *Deficient synthesis or liberation of acetylcholine at motor end-plates.* This is a popular theory and may well be the correct one, but it is difficult to prove or disprove. The work of Torda and Wolff⁵ would suggest that myasthenic serum contains a substance which inhibits the synthesis of acetylcholine. If this is so, it is strange that other cholinergic functions such as sweating, heart rate, visceral activity, etc., are not grossly affected in this disease. This work requires further confirmation. The beneficial effects claimed by one group of workers⁶ for administration of acetylcholine and other more stable choline esters to myasthenic patients has not been confirmed by our own experience. Further critical experiments with newer techniques may give the answer to this important question. (b) *Increased breakdown of acetylcholine due to overactivity of the enzyme cholinesterase.* It has been shown by a number of workers that blood cholinesterase is normal in myasthenia gravis.⁷ Muscle cholinesterase has also been found normal in the few cases where the determination has been made. (c) *Diminished sensitivity of muscle to acetylcholine.* Here we run into the confusing observation that myasthenic muscle, unlike curarized muscle, is actually hypersensitive to acetylcholine injected into the nutrient artery.⁸ This could mean, of course, that the two conditions are quite different in mechanism. On the other hand, curare poisoning is an acute affair whereas

myasthenia gravis is chronic. We know that denervation of a muscle results, after a couple of weeks, in increased sensitivity of the muscle to acetylcholine. Could it be possible that in myasthenia gravis some long-acting, curare-like substance produces a chemical denervation, with resulting sensitization of muscle to acetylcholine? No answer is at hand on this score. (d) *Presence of curare-like barrier at the neuromyal junction.* It has been reported that release of the tourniquet from an exercised limb in a myasthenic patient causes weakness of relatively unaffected muscles elsewhere in the body.⁹ The suggestion is that some curare-like substance has been released from the exercised muscle into the general circulation. These experiments are inconclusive, and in any event might point only to the release of normal metabolites with momentary effect on muscles elsewhere. It is tempting, too, to think of the thymus as perhaps elaborating some curare-like substance with resulting effect on the musculature throughout the body.

We have carried out a large number of experiments along this line.⁴ Extracts were made of large quantities of urine from nine patients with myasthenia gravis. These extracts were tested according to the classic frog method of Claude Bernard, and upon the cat's nerve-muscle preparation described by Briscoe. In only one instance could any curare-like effect be demonstrated. Similarly, experiments with defibrinated arterial and venous blood from myasthenic patients were negative. We have also had the opportunity of making extracts of two thymic tumors immediately after their removal by Eldridge Campbell from two patients with myasthenia gravis. No curariform activity could be demonstrated. It is always possible, of course, that these negative results might be due to improper methods of extraction or that the hypothetical curare-like substance might take effect slowly in terms of days or weeks as does, for example, the thyroid hormone. The rate of improvement of myasthenia gravis after thymectomy would tend to support this view. There is as yet, however, no experimental evidence that the thymus has a curare-like function, and the nearest clinical evidence consists in the somewhat encouraging results of thymectomy.

Thymectomy was first embarked upon in an organized way by Blalock of Johns Hopkins Hospital, and it has now been carried out by various surgeons in several hundreds of cases. Keynes has himself completed over one hundred thymectomies.¹⁰ He has summed up his results with the first hundred cases (1942-1947) as follows:

Patients assessed	63
Patients untraced	1
Patients recent	18
Patients died post-operatively	8
Patients with thymic tumors	10
	<hr/>
	100

Only one of the patients with thymic tumor showed improvement, and five had died by the end of the third post-operative month. These results are odd. In the sixty-three non-tumor patients whom Keynes assessed the results were as follows:

<i>Assessment</i>	<i>No.</i>	<i>Per Cent</i>
A. Well, No neostigmine	24	63
B. Almost well	16	
C. Better	18	29
D. No change	5	8

The Mayo Clinic experience has been summarized by Eaton.¹¹ He analysed results in fifty-two operated cases, of whom twenty had thymic tumors and thirty-two had no tumors. Results were compared with 128 control cases seen in the same period of time. All cases were studied for one year or longer before the evaluation was made. There were 8 per cent remissions in each group. However, 50 per cent of the operated group had shown unequivocal improvement while only 25 per cent of the control group had shown similar improvement.

Harvey¹² has reviewed the experience with 125 cases of myasthenia gravis at Johns Hopkins Hospital, of which thirty-two patients underwent thymectomy. His studies indicate that beneficial results are greater than might be expected from spontaneous remission.

It can only be said that in an encouraging number of cases there has been improvement, amounting in some instances to cure. The disturbing fact remains, however, that some patients are benefited little, and others not at all. This is hard to reconcile with the view that the thymus is primarily responsible.

Let our thoughts remain free, however. Let us reverse the field. What if the thymus is not producing a curarizing agent, but instead is becoming hyperplastic and forming adenomas in response to some need

—a need, perhaps, for increased synthesis of acetylcholine. This might explain Keynes' poor results after the removal of thymic tumors.

In this regard the occurrence of myasthenia gravis in a new-born baby is intriguing. We have studied a young woman with myasthenia gravis of several years' duration. Her thymus had been removed without benefit. Recently she was delivered of a child who had unmistakable signs of the same disease and who responded at once, and was kept alive by neostigmine.* We waited with bated breath to see whether the child's myasthenia would wear off. This it did by the thirty-fifth day, and neostigmine was no longer necessary. For two weeks the child swung in the opposite direction and became hypertonic. It then returned to a perfectly normal state. The mother died on the thirty-fifth post-partum day, apparently due to an increase of her myasthenia. What happened here? Did the mother pass some curarizing substance across the placenta to her child, or did she drain some precursor of acetylcholine from the child? Who knows?

Both ACTH,⁵ and cortisone appear to make the myasthenic patient worse during the period of administration. In the case depicted in Figure 2 cortisone had to be stopped on the fifth day due to severe increase of symptoms. This may be important in terms of mechanism. The adrenal cortical steroids have the effect of shrinking the thymus.

THYROIDAL NEUROMUSCULAR DISORDERS

Hyperthyroidism. Muscular weakness and fatigability may be prominent in uncomplicated hyperthyroidism. The mechanism is not clear but it seems likely that there is direct embarrassment of muscle metabolism. Certainly creatinuria is marked, and muscle isolated from a hyperthyroid animal uses much more oxygen than normal.¹³ In addition, however, there are a number of well-defined neuromuscular disorders which may co-exist with hyperthyroidism and which may be modified by it. A study of the inter-relationships between these conditions might well shed light upon them or upon the problems of muscular fatigue in man.

The following neuromuscular disorders which may appear with the hyperthyroid state are described briefly in order to emphasize the wide variety of mechanisms that may be involved:

* Geddes, A. K. and Kidd, H. M. Myasthenia syndrome of the newborn, *Canad. M.A.J.* to be published.

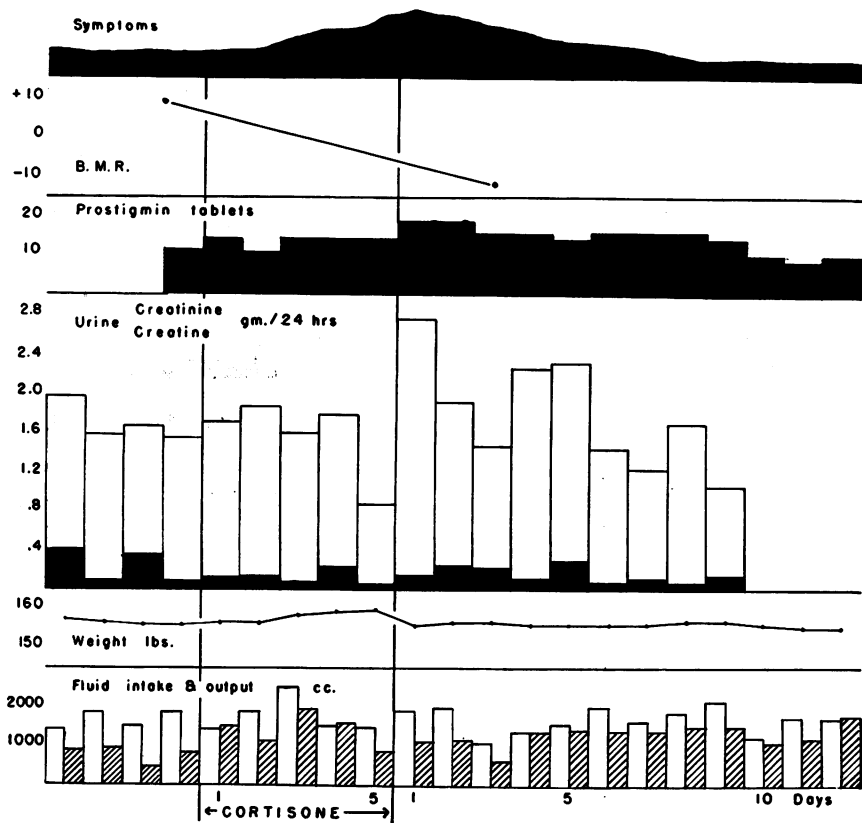


Figure 2—Effect of Cortisone in a case of myasthenia gravis.

(a) *Exophthalmic Ophthalmoplegia*. This consists in progressive protrusion of the eyeballs due to a dystrophic process affecting the extra-ocular muscles. There is edema, fatty infiltration and swelling of the muscle fibers. The condition is apt to appear, or to become aggravated, when the hyperthyroidism is brought under control. For this reason, and because of numerous experimental facts, the anterior pituitary thyrotropic hormone is suspect rather than the thyroid itself. No satisfactory medical treatment has been developed, and surgical decompression of the orbit may be necessary to preserve vision.

(b) *Acute Thyrotoxic Encephalomyopathy*. This jawbreaker title covers fairly completely a condition recently described in the Scandinavian literature. It results in a picture of bulbar palsy sometimes asso-

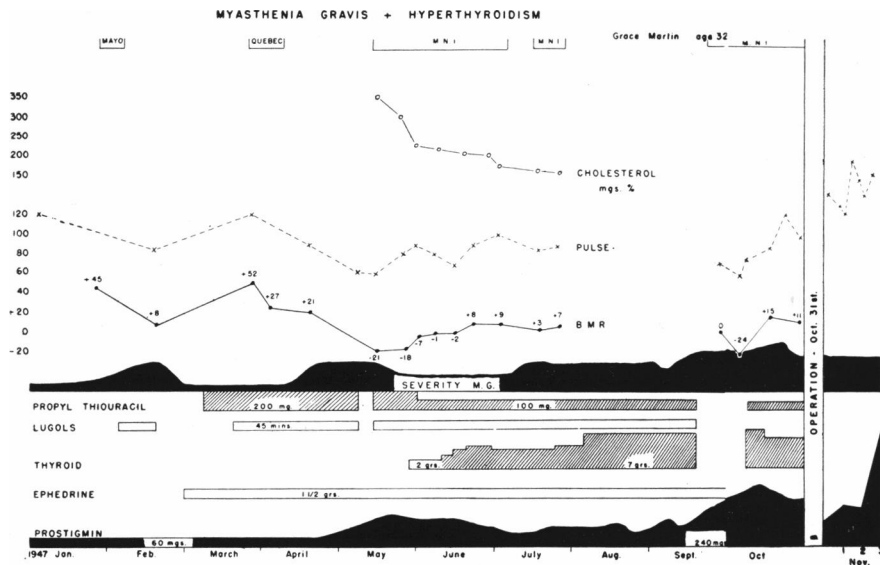


Figure 3—The inverse relationship between symptoms of myasthenia gravis and hyperthyroidism.

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ciated with Parkinson-like tremors and delirium or coma. It is relieved by treatment of the hyperthyroidism.

(c) *Chronic Thyrotoxic Myopathy* is characterized by generalized weakness, wasting and fasciculation of the voluntary muscles. This picture, which resembles so closely the incurable progressive muscular atrophy, vanishes after subtotal thyroidectomy.¹⁴ The condition is apt to occur in older people and without the usual florid evidences of hyperthyroidism such as goiter, exophthalmos or tachycardia.

(d) *Periodic Paralysis*. This condition is really a disorder of potassium metabolism in relation to neuromuscular function. Recurrent attacks of flaccid paralysis occur, lasting many hours and disappearing spontaneously. Attacks are associated with a fall of serum potassium and are rapidly terminated by administration of potassium salts. These bouts of paralysis are greatly increased in frequency and severity in the presence of hyperthyroidism or with thyroid feeding. In Shino-saki's¹⁵ series of twenty-four cases, seven had hyperthyroidism and eight simple goiter. In Tsuji's¹⁶ group of fourteen cases, eleven showed evidence of hyperthyroidism. Whether the so-called Basedow's para-

plegia described in the European literature represents the same thing is not clear.

(e) *Myasthenia Gravis*. The association of hyperthyroidism with myasthenia gravis has been reported rarely. We have assembled data from eight cases, including two of our own.¹⁷

Of the four instances in which myasthenia gravis appeared before the hyperthyroidism, the later appearance of hyperthyroidism brought unmistakable improvement of the symptoms of myasthenia. There seems to be an inverse, "see-saw" relationship between the two conditions—the myasthenia waning with the onset of hyperthyroidism or waxing with the treatment of the hyperthyroidism. This relationship was observed in both of our cases and was illustrated on five occasions in our second case, as shown in Figure 3.

Hypothyroidism. Myotonia has been repeatedly described both in cretin infants and in adults following thyroidectomy. The symptom is relieved by thyroid administration.

PROGRESSIVE MUSCULAR DYSTROPHY

In this condition the muscle fibers undergo slow degeneration with ultimate replacement by fat and fibrous tissue. The trunk, girdle and proximal limb muscles are mainly involved, while the distal muscles of hands and feet are relatively spared. Males are affected about five times as often as females. There is a strong tendency to familial involvement but many sporadic cases are seen.

In the past innumerable groupings have been made (e.g., fascio-scapulo-humeral, pseudohypertrophic, etc.) according to differences in the location of the wasting and age of onset. It does not seem profitable to perpetuate these nosologic refinements unless it can be shown that the groups differ from one another in the cause or mechanism of dystrophy. With our present knowledge the essential process appears to be similar in all, with an exception which we shall describe in a moment.

From the pathological viewpoint the process is confined to the muscles, and changes are not found in the other organs. In the early stages patchy degeneration appears, one affected fiber lying next to several normal ones. The combination of normal fibers with abnormal fibers in various stages of degeneration, down to actual fibrous or fatty replacement, is characteristic.

In sections made from muscle biopsies from our dystrophic patients marked changes in vascular patterns have been found. This is particularly noticeable in the fresh-teased preparations stained by gold chloride. The capillary anastomotic network is denser and more profuse than normal. Arterioles show thickening and proliferation of the medial coat and adventitia. Sometimes complete obliteration of the lumen is observed. It is not possible to say whether these vascular changes are primary or secondary to changes in the muscle fibers. We suspect that they are secondary.

It is of interest that Holman and Swanton¹⁸ produced degenerative lesions in the arteries of young dogs by a combination of renal injury and a deficient diet. It was found that addition of mixed natural tocopherols to the diet prevented the experimental necrotizing arteritis from appearing.

From the biochemical viewpoint, creatinuria is the most characteristic finding. Normally creatine output is about one-tenth that of creatinine in the normal adult male on a meat-free diet. It increases whenever there is a marked degree of muscle breakdown or wasting, from any cause, or with certain metabolic disorders. Creatinuria therefore serves as an index of the degree or nature of muscle involvement.

Hoagland and his co-workers,¹⁹ who have taken up the study some thirty-five years after the original discovery of creatinuria in progressive muscular dystrophy, consider it to be one of the most striking manifestations of the disease. More important is the diminished excretion of creatinine, which provides an even better indication of the severity of the disease than does creatinuria. In muscular dystrophy creatine tolerance is impaired and most of a dose of 1 to 3 Gm. of creatine fed by mouth is excreted in the urine. A normal individual would store all this creatine in the muscles and excrete none in the urine. It cannot yet be said whether the disturbance of creatine metabolism is merely an echo of muscle destruction or whether it plays a more primary and causative role. To some, creatinuria is to dystrophy what glycosuria is to diabetes.

The discovery that vitamin E deficiency in animals caused a form of muscle dystrophy, and that this could be prevented by wheat germ or tocopherols, led to great hopes.

From the beginning attempts were made by clinicians to discover the neuromuscular disease, in man, which might be the counterpart of

TABLE I

<i>Wheat Germ Oil</i>		<i>Improved</i>
Juvenile Muscular Dystrophy	25	5
Menopausal Myopathy	5	3
Dermatomyositis	3	3
Unclassified Muscular Atrophy	2	2
<hr/>		
Progressive Muscular Atrophy	11	0
Amyotrophic Lateral Sclerosis	14	0
Myasthenia Gravis	11	0
Miscellaneous	36	0
<i>Total</i>	107	

nutritional muscular dystrophy in animals. Therapeutic experiments were undertaken, but some of the early reports of improvement of muscular dystrophy and of amyotrophic lateral sclerosis were over-exuberant and uncritical. Numerous workers have now published negative results in muscle dystrophy and amyotrophic lateral sclerosis.

We present our own experience since it seems to be the most extensive recorded and covers 107 patients with various neuromuscular diseases, some of whom have been under study since 1936.

Wheat germ oil, Milhorat fraction of wheat germ oil, and synthetic alphatocopherol have been used alone and in combination, and in doses as high as 300 mg. daily when computed in terms of alphatocopherol, although the average was less than this, approximating 60 mg. daily. As can be seen in Table I, of a total of 107 patients treated with wheat germ oil, no beneficial effects were observed in amyotrophic lateral sclerosis, myasthenia gravis, disseminated sclerosis and a number of other conditions.

There were thirteen patients in the series who, in our judgement, showed sufficiently striking improvement to warrant the conclusion that treatment was responsible. Two cases of atypical muscular atrophy and five cases of progressive muscular dystrophy (three pseudohypertrophic type and two adult type) showed improvement of symptoms. The two atypical muscular atrophy cases were adult women who had suffered motor neurone disease in early life with a later exacerbation at the involutional period. These are difficult to classify. Three of the

above patients underwent relapse upon discontinuing treatment and improved again when it was resumed. Three other cases, all of whom improved, were labeled as dermatomyositis and exhibited a rubbery kind of dystrophic process in the muscle along with scleroderma-like changes in the skin. Milhorat *et al.*²⁰ have described two cases of dermatomyositis improved by fresh wheat germ. Our remaining five patients, women at about the climacteric age, exhibited a proximal type of muscle weakness involving mostly shoulder and pelvic girdle muscles. Three recovered almost completely. We have called this menopausal muscular dystrophy. From our experience it is impossible to say whether alphatocopherol or other factors in wheat germ oil were responsible for the improvement, since wheat germ oil, sometimes supplemented by alphatocopherol, was used in all these successful instances.

There are difficulties in establishing a human counterpart to the neuromuscular disorder seen in animals with vitamin E deficiency. A similar disease in man might be chronic and might not respond dramatically to treatment. Further, one would have to postulate some fault of digestion or absorption of the vitamin, since many of these patients take a normal diet. It is of interest that vitamin E is relatively ineffectual when given parenterally to animals with nutritional muscular dystrophy. Recovery occurs, however, when tocopherol is given by mouth, indicating that the vitamin is conjugated or changed in some way during digestion to form the antidystrophic principle. Finally, there is a regrettable confusion in clinical reports as to whether pure alphatocopherol, mixed tocopherols, whole wheat germ, wheat germ oil or one of its fractions has been used. These substances are all lumped together as "vitamin E", whereas some of them contain little of it and others contain a variety of other substances that might be effective.

Wheat germ, so essential to the normal growth of the cereal, is entirely milled off in the making of flour—a situation analogous perhaps to the disappearance of B complex factors with the bran during the polishing of rice. One cannot help but feel that there may be a large and undiscovered territory for the use of wheat germ and its fractions in nutritional and perhaps in hormonal disease.

PERIODIC PARALYSIS

(a) *Familial Periodic Paralysis*. This rare disease is characterized by attacks of flaccid paralysis affecting mainly the muscles of the trunk

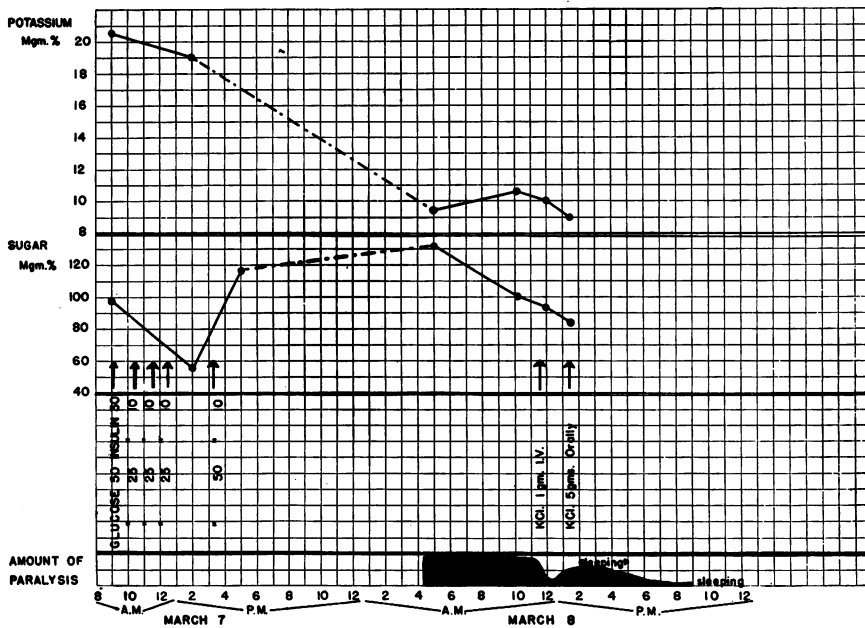


Figure 4—An attack of periodic paralysis induced by glucose and insulin.

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and limbs. The deep reflexes often disappear and the muscles become inexcitable to electrical stimulation. Attacks usually come on during sleep, and they last from a few hours to three or four days. In the intervals, muscular power is normal and the patient is entirely well. Attacks first make their appearance during childhood or adolescence and become less frequent, or disappear, in later life. Many theories have been advanced to explain these weird and crippling seizures.

The most comprehensive study of the disease has been made by Shinosaki¹⁵ who published his observations in twenty-four cases. Among the more important observations were the frequent (62 per cent) association of the disease with thyroid struma and the tendency for attacks to occur after administration of thyroid, epinephrine or diets high in carbohydrate. Hyperglycemia was often observed during the early stages of spontaneous attacks.

After some preliminary leads, a number of workers including ourselves pinned the condition down to a fault of potassium metabolism.²¹⁻²³

Attacks of paralysis are associated with a drop of the serum potassium level from the normal of 18-22 mg. per cent to as low as 5 mg. per cent, but there is no critical level for onset of muscular weakness. Recovery occurs rapidly when a potassium salt is given in adequate amount. There is nothing more dramatic in medicine, and the usual hoodoo of "hysterical paralysis" is quickly dissolved when the real mechanism is known. Figure 4 shows the events in an attack which was induced by glucose and insulin.

Attacks can be produced by the administration of epinephrine, glucose or adrenal cortical extract. All of these methods seem to involve the carbohydrate cycle. There is no diuresis of potassium prior to or during attacks. It seems that potassium is called from the blood to meet a need in the muscles.

Not all people with a low blood potassium develop paralysis. It is well known that some diabetics under insulin-glucose therapy show a sharp drop in serum potassium. Muscular weakness develops in some, however, and potassium is now included in the armamentarium for treating diabetic coma. In other words, some patients in diabetic coma are suffering too from periodic paralysis. Overtreatment of Addison's disease with D.C.A. (desoxycorticosterone acetate) may also cause a fall in serum potassium. We have seen several cases with no paralysis despite a serum potassium level below 10 mg. per cent. Ferrebee *et al.*²² described the equivalent of periodic paralysis in dogs subjected to large doses of D.C.A. In essence, there may be some fault of muscle metabolism too in those who develop profound paralysis with the fall in blood potassium. Several patients subject to periodic paralysis have shown persistent creatinuria in between attacks.

Hubert Jantz,²⁴ in a study of nine cases of periodic paralysis, found that between attacks all of the serum potassium was ultrafiltrable but during the paralysis only a portion, sometimes less than half, was found in the ultrafiltrate. The potassium concentration of muscle, taken by biopsy during the height of a severe attack, was 710 mg. per 100 Gm. Another muscle sample taken from the same patient 30 minutes after recovery contained 360 mg. per 100 Gm. It seems that skeletal muscle, under some circumstances, has a need for more potassium and that it then drains the blood of its supply. This mechanism must surely operate to some extent in health, and perhaps in a wide variety of metabolic states that lead to minor fatigue and weakness. Jantz thinks that lack

of ionized potassium inhibits the normal cleavage of creatine phosphate in muscle. If correct, this would do more to explain the mystery of periodic paralysis than anything yet.

(b) *Sporadic Periodic Paralysis*. We think that this occurs quite often, but is hard to prove. One patient with no familial history had definite attacks of periodic paralysis. Some mornings weakness of the limb muscles was so great that he could not put on his coat or shave unassisted. Serum analysis at the time of weakness showed a low potassium level (13 mg. per cent) and this returned to normal, and muscle power too, after administration of potassium chloride by mouth. An interesting finding grew out of this. The patient had learned by experience that going out "with the boys for a beer" the night before prevented any muscular weakness from appearing the next day. A request for information from the Black Horse Brewery showed that one quart of the favorite ale contained the equivalent of one gram of potassium chloride. This is not a plug for Canadian ale, for I understand that American brands are equally able to cure certain kinds of paralysis. All beer is high in potassium and, for those of you interested in treating diabetes, orange juice is too.

We have examined two girls in their early teens, each of whom suffered rapid onset of generalized muscular paralysis within a few hours. Both had recovered at the time of the examination, 24 to 48 hours later. In each instance no residual sign of central nervous system defect could be found. We suspect these were isolated episodes of periodic paralysis. Both young women developed symptoms following exposure to cold, and both at the time of a menstrual period. Shinosaki showed that exposure to cold led to attacks of periodic paralysis in some of his cases. Minor instances of periodic paralysis should be sought for in many metabolic upsets where asthenia, stiffness and aching of muscles are a transitory complaint.

Harvey¹² has pointed out that both hypo-potassemia, as shown above, and hyper-potassemia, as met with in some cases of renal failure, may cause muscular weakness and dysfunction, and that a guide to proper therapy may lie in the T wave change of the electrocardiogram which is a sensitive indication of the serum potassium level. Even with the rapid method of determining serum potassium by the flame-photometer, the time lag is too long in these urgent cases and the electrocardiogram is the best running guide.

As shown before, attacks of paralysis can be readily induced in the patient subject to periodic paralysis. One of the simplest means is to administer successive doses of glucose and insulin. This led to the suspicion that some patients being vigorously treated for diabetic acidosis might develop hypo-potassemia. The suspicion proved true. As shown in an excellent exhibit in the Academy tonight, about 20 per cent of such patients develop hypo-potassemia of sufficient degree to cause symptoms or signs.

Nadler and his associates²⁵ administered potassium to forty-nine patients with hypo-potassemia; twenty-five were undergoing treatment for diabetic acidosis, and twenty-four had intestinal obstruction associated with prolonged vomiting. The potassium deficit was further increased since many of these patients received parenteral fluids from which potassium was omitted. Three of the diabetic patients showed skeletal muscle flaccidity, lowered blood pressure, bounding pulse and a loud systolic murmur. The other patients showed only minor degrees of these manifestations, the most prominent of which were skeletal muscle weakness and/or a decrease in the blood pressure, particularly the diastolic component. Determination of serum potassium was made by the flame photometer. Although the chemical method is of value it was not always practical for repeated determinations. Therefore serial electrocardiograms were made. Prolongation of the Q-T interval with widening of the T wave and lowering or inversion of the T wave (CR₃) were used to estimate the serum potassium concentration.

There is an indication, too, that some patients undergoing insulin shock therapy, who do not recover consciousness when glucose is given, may be suffering from hypo-potassemia. They may recover when potassium is administered.

Hypo-potassemia, then, is a mechanism which may operate in many conditions. We should thank the dramatic grandmother—periodic paralysis, for drawing our attention to it, and we should start to look for the grandchildren who will now begin to make their appearance in many fields of medicine.

MENOPAUSAL MUSCULAR DYSTROPHY

And now, in conclusion, I would like to direct your attention to a form of muscle dystrophy that occurs in later life and which we have named Menopausal Muscular Dystrophy. I have described how three

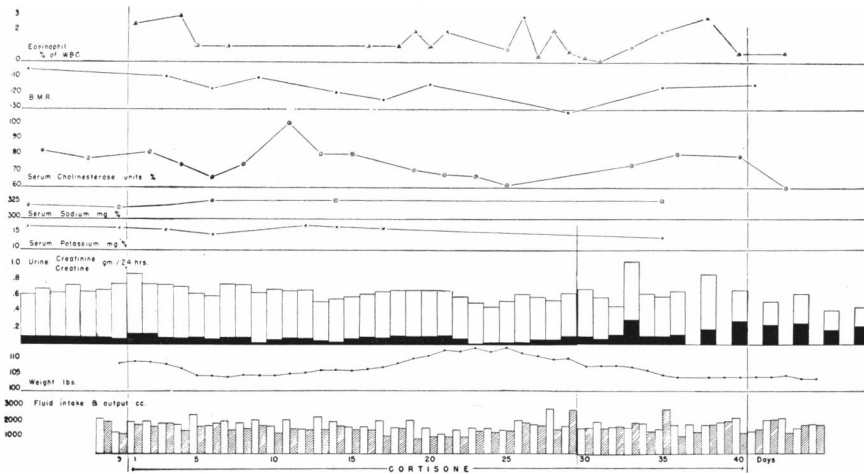


Figure 5—Menopausal muscular dystrophy treated with Cortisone. Creatinuria is not a feature.

out of five earlier cases responded to wheat germ oil therapy. We now find, however, that the response to cortisone can be much more rapid and dramatic, and that the hormone may spell the difference between invalidism and useful activity for these people.

This dystrophy appears gradually, or sometimes rapidly, in the late forty's or thereafter. Women are usually affected, but we have had two men with the condition. There is symmetrical weakness of the girdle muscles, especially those of the hip girdle. This results in the three most characteristic symptoms of the disease: a) inability to rise from a chair unassisted, b) difficulty in climbing stairs, and c) a tendency to unpredictable falls. Since there is no evident wasting, and since deep reflexes are usually intact, the condition is apt to go unrecognized or to be attributed to the enfeeblement of age. Marked creatinuria is not a feature in these cases and it has been a source of disappointment to us that successful treatment with cortisone has not led to any appreciable change in creatine or creatinine output (Fig. 5).

Patients with this condition may respond dramatically to cortisone. Beginning about the fifth day after institution of treatment there is a feeling of increased strength and a perceptible increase in muscle power. One patient on admission, for instance, could climb only five steps in 20 seconds by pulling herself up the railing. After eighteen days of

cortisone therapy she could climb forty steps in the same time without the use of her hands. Other manifestations improve in like manner, and patients may get out and do their shopping for the first time in many months.

At the present time we have six patients with this trouble who are on maintenance doses of cortisone. The average amount necessary to hold them is 75-150 mg. three times a week. When you begin to economize with the cortisone the patient will soon complain. This substance is as necessary to them as insulin is to the diabetic.

We have met with no serious complications in the use of cortisone. The dosage has been usually 100 mg. daily during an active treatment period of up to thirty-five days. A skin eruption appeared in one patient. A lowered glucose tolerance occurred in all, but no glycosuria was met with. No psychoses appeared, and not one out of a consecutive series of sixteen patients showed any change in the E.E.G. This is different from the finding of Hoefer and Glaser with ACTH. The latter substance, of course, calls out many other adrenal hormones in addition to cortisone.

The pathological change in menopausal dystrophy consists in a spotty degeneration and sometimes necrosis, with nearby muscle fibers perhaps unaffected. There may be an increase of sarcolemmal nuclei. In chronic lesions the blood vessels may be thickened, but in general the interstitial reaction is not great. It may be of interest, since we are considering possible mechanisms tonight, that the above picture resembles closely that described by Pappenheimer and others²⁶ in animals suffering from vitamin E deficiency.

And now, in closing, may I thank you for your attention. May I also express with you the hope that a further knowledge of these mechanisms may soon lead to practical relief for the many who suffer from disorders of muscle function.

REFERENCES

1. McEachern, D. and Rabinovitch, R. Advances in the neuromuscular disorders, *Advances in Internal Medicine*, 1950, 4:201.
2. Brown, G. L. and Harvey, A. M. Congenital myotonia in the goat, *Brain*, 1939, 62:341.
3. Kennedy, F. and Wolf, A. Experiments with quinine and prostigmin in treatment of myotonia and myasthenia, *Arch. Neurol. & Psychiat.*, 1937, 37:68.
4. McEachern, D. The thymus in relation to myasthenia gravis, *Medicine*, 1943, 22:1.

5. Torda, C. and Wolff, H. G. Effects of adrenocorticotrophic hormone on neuromuscular function in patients with myasthenia gravis, *J. Clin. Investigation*, 1949, 28:1228.
6. Fraser, F. R., McGeorge, M. and Murphy, G. E. Action of choline esters in myasthenia gravis, *Clin. Sc.*, 1937, 3:77.
7. Odom, G., Russel, C. K. and McEachern, D. Studies of neuromuscular disorders: the myogram, blood cholinesterase and effect of prostigmin in myasthenia gravis and progressive muscular atrophy, *Brain*, 1943, 66:1.
8. Lanari, A. Myasthénie grave et transmission chimique neuro-humorale, *Compt. rend. Soc. de biol.*, 1937, 126: 827; also in Spanish in *Rev. Soc. argent. de biol.*, 1937, 13:299.
9. Walker, M. B. Myasthenia gravis; case in which fatigue of forearm muscles could induce paralysis of extraocular muscles, *Proc. Roy. Soc. Med.*, 1938, 31:722.
10. Keynes, G. *Conference on Myasthenia gravis*, Massachusetts General Hospital, Oct. 1947.
11. Eaton, L. M. *Personal communication*, March 1948.
12. Harvey, A. M. Some preliminary observations on the clinical course of myasthenia gravis before and after thymectomy. *Bull. New York Acad. Med.*, 1948, 24:505.
13. McEachern, D. The metabolism of isolated surviving tissues from animals rendered hyperthyroid with thyroxine, *Bull. Johns Hopkins Hosp.* 1935, 56: 145.
14. McEachern D. and Ross, W. D. Chronic thyrotoxic myopathy, *Brain*, 1942, 65: 181.
15. Shinosaki, T. Klinische Studien über die periodische Extremitätenlähmung, *Ztschl. f. d. ges. Neurol. u. Psychiat.*, 1925-26, 100:564.
16. Tsuji, K. Ueber die Pathogenese der paroxysmalen Extremitätenlähmung, *Klin. Wchnschr.*, 1939, 18:320.
17. McEachern, D. and Parnell, J. L. Relationship of hyperthyroidism to myasthenia gravis, *J. Clin. Endocrinol.*, 1948, 8:842.
18. Holman, R. L. and Swanton, M. G. "Dietary factor" in necrotizing arteritis in dogs a lipid substance, *Proc. Soc. Exper. Biol. & Med.*, 1946, 63:87.
19. Hoagland, C. L., Gilder, H. and Shank, R. E. Synthesis, storage and excretion of creatine, creatinine and glycochamine in progressive muscular dystrophy and the effects of certain hormones on these processes, *J. Exper. Med.*, 1945, 81:423.
20. Milhorat, A. T., Toscani, V. and Bartels, W. E. Effect of wheat germ on creatinuria in dermatomyositis and progressive muscular dystrophy, *Proc. Soc. Exper. Biol. & Med.*, 1945, 58:40.
21. Aitken, R. S. Allott, E. N. Castleden, L. I. M. and Walker, M. Observations on a case of familial periodic paralysis, *Clin. Sc.*, 1937, 3:47.
22. Ferrebee, J. W., Atchley, D. W. and Loeb, R. F. Study of the electrolyte physiology in a case of familial periodic paralysis, *J. Clin. Investigation*, 1938, 17:504.
23. Pudenz, R. H., McIntosh, J. F. and McEachern, D. The role of potassium in familial periodic paralysis, *J.A.M.A.*, 1938, 111:2253.
24. Jantz, H. Stoffwechseluntersuchungen bei paroxysmaler Lähmung, *Nervenarzt*, 1947, 18:360, abstract in *Chem. Abstracts*, 1948, 42:8942.
25. Nadler, C. S., Bellet, S., and Gazes, P. C. Administration of potassium to patients with prolonged vomiting and diabetic acidosis, *J. Lab. & Clin. Med.*, 1950, 35:842.
26. Pappenheimer, A. M. The pathology of nutritional muscular dystrophy in young rats, *Am. J. Path.*, 1939, 15:179.